Cholesterol Metabolism Is a Druggable Axis that Independently Regulates Tau and Amyloid-beta in iPSC-Derived Alzheimer's Disease Neurons.

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Public Summary:
Genetic, epidemiologic, and biochemical evidence suggests that predisposition to Alzheimer's disease (AD) may arise from altered cholesterol metabolism, although the molecular pathways that may link cholesterol to AD phenotypes are only partially understood. Here, we perform a phenotypic screen for pTau accumulation in AD-patient iPSC-derived neurons and identify cholesteryl esters (CE), the storage product of excess cholesterol, as upstream regulators of Tau early during AD development. Using isogenic induced pluripotent stem cell (iPSC) lines carrying mutations in the cholesterol-binding domain of APP or APP null alleles, we found that while CE also regulate Abeta secretion, the effects of CE on Tau and Abeta are mediated by independent pathways. Efficacy and toxicity screening in iPSC-derived astrocytes and neurons showed that allosteric activation of CYP46A1 lowers CE specifically in neurons and is well tolerated by astrocytes. These data reveal that CE independently regulate Tau and Abeta and identify a druggable CYP46A1-CE-Tau axis in AD.

Scientific Abstract:
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